Remarks

Prior to entry of this amendment, claims 1-28 were pending in the application. Of these, claims 16-19 and 24-28 are withdrawn from consideration as drawn to non-elected Groups. Thus, claims 1-15 and 20-23 are currently under examination (of which claims 1-15 are considered linking claims and claims 20-23 correspond to elected Group III).

By this amendment, claims 1, 3, 9, 27 and 28 are amended. New claims 29-40 are added; claims 29-32 contain subject matter originally in claim 3, while claims 33-36 contain subject matter originally in claim 28. It is believed that claims 33-37 belong in elected Examiner's Group I, and that they therefore will be withdrawn.

Support for the amendments to the claims can be found throughout the specification and the claims as originally filed. Representative support for the phrase "treating a subject having a medical condition associated with the cardiovascular system" (now in claim 1) can be found, for instance, in the specification at page 2, lines 30-31. Representative support for the phrase "wherein the administration is by a route selected from the group consisting of intravenous injection, intramuscular injection, oral, buccal, rectal, *ex vivo*, intraocular, intraperitoneal, intravenous, intraarterial, subcutaneous, inhalation, intramuscular, and into a cardiopulmonary bypass circuit" (now in claim 1) can be found, for instance, in original claims 9 and 10 as well as in the specification at page 7, lines 26-28; page 11, line 15; page 12, lines 28-30; page 13, lines 23-24 and lines 31-35; page 17, line 2; Section VIII (which begins on page 22; including specifically page 22, line 36-37; page 23, lines 25 and 32; page 24, lines 1-8 and 15-20; Example 1 (*e.g.*, page 25, line 3) and so forth. Claim 9 is amended to correct an obvious clerical error, and to remove the term "parental" so that dependence from claim 1 is correct. Claim 27 is amended to correct a clerical error. Claims 37 and 38 are supported for instance in original claim 6, as well as in the specification at page 16, lines 10-13. Claims 39 and 40 are supported at least by original claim 10, for instance.

No new matter has been added by any of these amendments. Applicants reserve the right to pursue at a later date any subject matter deemed to be removed by this amendment.

After entry of this amendment, **claims 1-40 are pending in the application, of which 1-15, 20-23, and 29-40 are believed to be under examination**. Consideration, rejoinder (where appropriate) and allowance of the claims is respectfully requested.

Examiner Interview

Applicants thank the Examiner for granting a telephone interview on July 22, 2008. Present on the telephone were Examiner Arnold and Applicants' undersigned representative, Tanya Harding. Applicants acknowledge receipt of the Examiner's Interview Summary dated July 28, 2008.

All of the pending rejections were discussed, at least briefly. Applicants' representative proposed arguments and, in some instances, amendments (provided to the Examiner in advance of the interview) in response to the rejections, which the Examiner indicated he would consider once a response was formally submitted. While complete agreement was not reached on all matters, Applicants believe this response and the amendments submitted herewith have been prepared in accordance with the discussion and the suggestions made by the Examiner.

Applicants' representative also drew the Examiner's attention to Lauer *et al.* (2001), entitled "Plasma nitrite rather than nitrate reflects regional endothelial nitric oxide synthase activity but lacks intrinsic vasodilator action"; this article was provided to the Office in the Information Disclosure Statement dated May 3, 2006. As noted in the Examiner's Interview summary and discussed more fully herein, this reference teaches that "physiological levels of nitrite are vasodilator-inactive" (quoting the last sentence of Lauer *et al.* abstract). Lauer *et al.* further claim: "The complete lack of vasodilator activity of intraarterial infusion of nitrite clearly rules out any role for this metabolite in NO delivery." (Page 12818 at the bottom right.)

Restriction Requirement

Applicants acknowledge that the election of Group III was made without formal traverse. However, a specific error in the Restriction Requirement was pointed out by Applicants (contrary to the statement made on page 2 of the current Office action). As detailed in Applicants' response submitted on January 28, 2008, the Examiner had previously

acknowledged (in a telephone interview on January 17, 2008) that claims 24-28 belong with Group I rather than Group III, as was indicated in the Restriction Requirement. Applicants request that the Examiner please acknowledge the correct Group assignment of claims 24-28 (and newly added claims 33-36) in the next written document in this file.

Claim Rejection -- §112, 2nd paragraph

Claim 3 is rejected as allegedly indefinite for including a broad recitation ("about 25% methemoglobin") and lesser amounts that are narrower statements of the range/limitation. To expedite prosecution, Applicants have amended claim 3 to include only "about 25% methemoglobin", and new claims 29-32 are submitted herewith directed the lesser amounts originally included in the alternative in claim 3. It is believed that this fully addresses this rejection, and Applicants therefore request its withdrawal.

Applicants have also amended claim 28, and provide corresponding new claims 34-36, to remove a similar list from the claims.

Claim Rejections -- §102

Claims 1-4, 6-9, and 11-13 are rejected as allegedly inherently anticipated by Henderson *et al.* (1972), as evidenced by "Hot dog nutrition facts". Applicants traverse this rejection, and request that it be withdrawn.

The noted claims are rejected on the basis of Henderson *et al.* teaching that ingestion of hot dogs and, allegedly, a sodium nitrite solution, causes headaches. The headaches might be caused by vasodilation, which the Office attributes to sodium nitrite. Absent evidence to the contrary, the Office has assumed that the ingested sodium nitrite as applied in Henderson *et al.* inherently induces vasodilation. The burden has therefore been placed on Applicants to show that the claimed method differs from Henderson.

To anticipate the invention, a prior art reference "must disclose each and every feature of the claimed invention, either explicitly or inherently. (*See*, for example, *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.* 471 F.3d 1369 (Fed. Cir. 2006)). In addition, Section 2112(IV) of the

MPEP states that an "Examiner must provide rationale or evidence tending to show inherency." "The mere fact that certain thing may result from a given set of circumstance is not sufficient."

Applicants submit that Henderson does not disclose each and every feature of the claimed invention. Further the Office has not provided evidence to support inherency as required by MPEP Section 2112. The claims as presented herein are distinct from the Office's interpretation of the Henderson *et al.* reference *at least* because that reference does not teach a method of administering any compound (including for instance a nitrite salt) for the purpose of treating a subject for a medical condition associated with the cardiovascular system. Henderson *et al.* at best suggest that ingested sodium nitrite may cause headaches in a subject (in some instances). The Office has not provided any basis in fact or technical reasoning to support the allegation that *treatment* of a medical condition "necessarily flows from the teaching" of Henderson *et al.* (MPEP 2112). If Henderson *et al.* teach anything of relevance to Applicants' application, it is that nitrite salt *causes* a medical condition. Certainly nothing in Henderson *et al.* teaches the administration of sodium nitrite (or hot dogs) to "a subject having a medical condition that would benefit from vasodilation or increased blood flow…," which is included in Applicants' current claims.

Because Applicants' claims are clearly distinguished from Henderson *et al.*, there is no need to address the Office's assumptions that all elements in the rejected claims can be found in the Henderson reference.

Thus, Applicants request that this rejection be withdrawn in view of the above comments and amendments made herein.

Claims 1-4, 6-8, 11, and 12 are rejected as allegedly anticipated by Gale (US 4,849,226). Applicants traverse this rejection, and ask that it be withdrawn.

The Office alleges that Gale describes a bandage that is applied to skin in order to provide application of a vasodilator. At column 6, line 54-55, Gale indicates that sodium nitrite might be included in their bandages (though Applicants note that the only allegedly therapeutic

compound actually used in the Gale bandages is nitroglycerine). Absent evidence to the contrary, the Office has assumed that all elements in Applicants' claims can be found in the teachings of Gale – and particularly that the sodium nitrite referred to in Gale is non-acidified.

Applicants' now-pending claims are distinct from the teachings in Gale at least because Gale only contemplates **topical or transdermal delivery to the skin** (see, *e.g.*, column 2, lines 8-18, 55-60, and throughout the Gale patent). The present claims do not encompass topical or transdermal delivery to the skin. Additionally, one of skill in the art, reviewing Gale at the time of Applicants' priority date, would not have believed that sodium nitrite could be absorbed through the skin because nitrite is a negatively charged salt, which requires transport mechanisms to cross the skin.

Because the now-pending claims are clearly distinguished from the teachings in Gale, there is no need to address the assumption of the Office that all elements in Applicants' claims can be found in the teachings of Gale.

Applicants request that this rejection be withdrawn in view of the above comments and amendments made herein.

Claim Rejections -- §103

Claims 1-15 and 20-23 are rejected as allegedly obvious over Zhang *et al.* (1994) in view of Modin *et al.* (2001), and also in view of Nachtscheim (1998) with respect to claims 13-15. Applicants traverse these rejections, and ask that they be withdrawn in light of the following arguments.

The Office alleges that Zhang teaches the use of nitric oxide (NO) donors to increase blood flow in rats to reduce brain damage due to focal ischemia; that Modin teaches that (i) NO is derived from nitrite in rats and (ii) non-acidified sodium nitrite causes vasodilation; and that Nachtsheim teaches that the known vasodilator, sildenafil, works in conjunction with NO to enhance vasodilatory effect. According to the Office, it would have been obvious to use the non-acidified sodium nitrite allegedly taught by Modin in the method of Zhang to produce

Applicants' claimed invention. With respect to claims 13-15, which deal with a combination of sodium nitrite and another agent, the Office alleges it would have been obvious to add sildenafil to the sodium nitrite to enhance the effect, as taught by Nachtsheim.

First, "nitric oxide donors" (as that phrase is used in Zhang and other references) are different from inorganic nitrites (salts) such as sodium nitrite. The only difference the Office points to with respect to Zhang and the present invention is that Zhang does not teach non-acidified sodium nitrite in the amount of 0.6 to 240 μM. The Office then states that this defect is cured by Modin. By doing so, the Office overlooks significant distinctions between Zhang and Modin, as well as the present invention: "**nitric oxide donors" and sodium nitrite are not equivalent substitutes for each other**.

Zhang describes use of "nitric oxide donors", *i.e.*, sodium nitroprusside (SNP) and 3-morpholino-sydnonimine (SIN), in its experiment with rats. Applicants' claims, and the work described by Modin, employ sodium nitrite, *i.e.*, an inorganic nitrite. Nitric oxide donors and inorganic nitrite are structurally dissimilar and they form NO in different manners. Compare the molecular formulas for each:

Sodium nitrite	$NaNO_2$
SNP	$Na_2[Fe(CN)_5NO]\cdot 2H_2O$
SIN	$C_6H_{11}N_4O_2\cdot Cl$

The Office must provide evidence that one of ordinary skill would have had a reasonable expectation that an inorganic nitrite salt (such as sodium nitrite) is an equivalent substitute for the structurally dissimilar SNP or SIN. No such evidence is on record, nor do Applicants know of any such evidence.

Moreover, when SNP breaks down it releases NO and cyanide. In contrast, inorganic nitrite is not comprised of cyanide ions and does not "release" NO in the same way SNP does. (In fact, sodium nitrite is an antidote for cyanide poisoning.) Given the significantly different structures and different mechanisms of generating NO, the Office must provide evidence that one of ordinary skill would have a reasonable expectation that sodium nitrite could be used as an equivalent substitute for SNP or SIN.

Thus, contrary to the statement in the pending Office action at page 8, first paragraph, one of skill in this art would *not* have had a reasonable expectation that the inorganic nitrite of Modin could successfully substitute for the nitric oxide donors used by Zhang.

Second, Modin teaches that **acidified** inorganic nitrite is preferred. Even if, for the sake of argument, the compound used by Modin was deemed a reasonable substitute to the compound used by Zhang (which Applicants do not admit), there is no credible support for an allegation that one of skill would have used the (allegedly) non-acidified sodium nitrite of Modin in the method of Zhang.

The clear teaching of Modin, as acknowledged in the Office's summary of Modin, is that inorganic nitrite is a more effective vasodilator in an acidic environment as compared to a non-acidic environment. Thus, if one of ordinary skill in this art were to consult Modin in relation to Zhang, the only potentially reasonable conclusion to draw from Zhang would be to use the "nitric oxide donor" in an acidic environment, as it is more efficient. In other words, why would one of ordinary skill in this art choose the *least effective pH* from Modin to apply to the Zhang teaching, *i.e.*, non-acidified or neutral pH?

Third, the studies of Modin were conducted in aortic ring bioassays without circulating blood. These studies are qualitatively not different from similar work performed by Robert Furchgott in 1952 (Furchgott & Bhadrakom, *J Pharmacol Exp Ther* 108(2):129-43, 1953; a copy of this reference is provided in the IDS submitted herewith, for the Examiner's convenience). These experiments were all performed in **isolated** aortic rings without blood in them. Because these studies required extremely low oxygen tension and low pH, as well as high nitrite concentrations, these experiments were not considered by those of skill in the art to reflect what would happen in the human circulation, as evinced for instance by the Lauer paper described below. It has now been clearly shown by Isbell *et al.* that oxygenated blood inhibits the nitrite induced vasodilation of aortic rings (*Am J Physiol Heart Circ Physiol* 293(4):H2565-72, 2007); a copy of this reference is provided in the IDS submitted herewith, for the Examiner's convenience.

Fourth, Applicants note that the art prior to Applicants' invention taught that **inorganic nitrite (particularly sodium nitrite) did not have vasodilatory effect *in vivo***. Art available as of the priority date of the present application taught that administration of pharmaceutical levels of nitrite to human subjects *in vivo* did not induce vasodilation and/or increase blood flow. This is discussed, for instance, at page 2, lines 4-13 and page 21, lines 29-33 of the present specification, and is further described below.

Because of the low potency of nitrite in aortic rings without acidification (see, *e.g.*, Modin and Furchgott), and the effects of blood on inhibiting NO, the state of the art as of the priority date of Applicants' filing was that nitrite was not a vasodilator in the human circulation system, particularly at concentrations less than 200 μM. This is made abundantly clear in the Lauer study (Lauer *et al.*, *PNAS* 98:12814-12819, 2001), which was discussed with the Examiner during the interview. Even the title of the Lauer study claims that "nitrite lacks intrinsic vasodilator action". On page 12816, at the bottom right paragraph, the authors indicate: "Intraarterial application of nitrite was found to be devoid of vasodilator activity at doses up to 36 μM/minute. Venous plasma nitrite concentrations achieved at the highest dose level exceeded 130 μM and were thus approximately 200 times greater than the concentrations measured during maximal eNOS stimulation with Ach." On page 12818 at the bottom right, the authors further claim: "The complete lack of vasodilator activity of intraarterial infusion of nitrite clearly rules out any role for this metabolite in NO delivery."

Further, Lauer *et al.* concluded that "[i]ntraarterial application of nitrite ($NaNO_2$ in 0.9% saline) was found to be devoid of vasodilator activity at doses up to 36 μmol/min (tested range: 0.01-36 μmol/min; n = 3)" (Lauer at page 12816, right column, last paragraph). Similarly, Rassaf concluded that "...the application of exogenous nitrite and nitrate at doses equimolar to those of NO did not exert dilation at all..." (Rassaf *et al.*, *J. Clin. Invest.*, 109:1241-1248, 2002, at page 1245, 1st column, 2nd paragraph). (Copies of both Lauer and Rassaf were previously made of record in this file.)

Thus, one of skill in the art reading Lauer, Russaf and Modin, would conclude that aortic ring bioassays are a poor method to use to study or characterize the *in vivo* vasodilatory effects of sodium nitrite. Further, based on the *in vivo* teachings of Lauer and Rassaf related to inorganic nitrite and vasodilation, the skilled artisan would not have expected sodium nitrite to have a beneficial therapeutic effect when administered, for instance by injection, to a subject to induce vasodilation or increase blood flow, regardless of the *in vitro* results in rat aorta provided by Modin. This was the accepted state of the art of the field – which is evidenced further by Applicants' research corresponding to the subject application having been published in *Nature Medicine* – such publication **requires** that the research be new.

Applicants also note that there was strong resistance in the art to their work, approaching the level of ridicule by others in the field – reflective of there being absolutely nothing obvious about Applicants' invention. See, for instance, the set of Letters to the Editor published in *The New England Journal of Medicine* on July 24, 2003 (349:402-405; provided to the Office previously), comment on Applicants' earlier work (Schedhter & Gladwin, *N Engl J Med* 348:1483-1485, 2003). By way of example, McMahon (at page 403) indicates "The suggestion that nitrite (at native concentrations) causes vasodilation in humans has been refuted experimentally." (Citing Rassaf *et al.*, 2002). It is clear on the record that those of ordinary skill in the art did not consider sodium nitrite, or any other inorganic nitrite salt, to have *in vivo* vasodilatory activity.

Given the above arguments, including (1) distinctions between nitrite salts and the nitric oxide donors of Zhang, (2) Modin's 'teaching away' from non-acidic nitrite solutions, (3) the inability to predict from an *in vitro* system such as Modin's to the subject *in vivo* system, and (4) the art teaching that infusion of nitrite into humans *in viv*o does not induce vasodilation, the combination of Zhang and Modin does not make the present invention obvious. Without Zhang and Modin, the rejection of claims 13-15 on the basis of Nachtsheim cannot stand. Applicants request that the rejections of claims 1-15 and 20-23 as allegedly obvious be withdrawn.

Double Patent Rejection

Claims 1, 6-13 and 20-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-4, 11, and 13-15 of copending Application No. 10/563,683. Without admitting to the properness of this rejection, Applicants ask that it be held in abeyance until the claims of one case or the other are allowed.

Request for Rejoinder

Based on the Restriction Requirement dated December 12, 2007, Applicants note that claims 1-15 are linking claims across the three Groups assigned by the examiner. Thus, the requirement for restriction to one of the linked Groups is subject to the non-allowance of linking claims 1-15. Once any of the linking or bridging claims is found to be allowable, the currently withdrawn claims of other Groups (Group I – claims 16, 18, and 24-28 (and claims 33-36); and Group II – claims 17 and 19) will be recombined and examined in the subject case. Such action is respectfully requested.

Similarly, Applicants understand that those portions of claims directed to non-elected species will be rejoined in the present application upon allowance of a claim generic for the species. Such action is respectfully requested.

Observations on Nathanson (U.S. Patent No. 5,500,230)

In the July 28, 2008 Interview Summary, it is noted that the Examiner alerted Applicants to U.S. Patent No. 5,500,230 (Nathanson). Applicants have taken this opportunity to review Nathanson, and provide the following brief comments based on their observations.

Nathanson appears to teach "topical use of hydralazine, non-organic nitrites or nitroglycerine, and the systematic use of hydralazine or non-organic nitrites" to treat "cranial fluid volume dysfunctions such as glaucoma..." (Abstract). Nathanson goes on to define the term "cranial fluid volume dysfunction" as "those pathological conditions associated with an overproduction or decreased rate of removal of fluid from the cranium including the eye." (Column 5, lines 53-64). The Nathanson technology is clearly distinguishable from Applicants' claimed invention. For instance, nowhere in Nathanson is it taught that any compound can be

used to treat a subject having a medical condition associated with the cardiovascular system, particularly where the treatment induces vasodilation and/or increases blood flow in the subject.

In addition, Nathanson **explicitly** teaches that compounds he is using do not decrease or otherwise influence blood pressure – they have absolutely no vasodilatory effect. See, for instance, Column 4, lines 12-15; the legend for Figure 14 (Column 5, lines 25-29); and Column 13, lines 8-12. This is completely contrary to Applicants' invention, and if anything would have led one of ordinary skill away from Applicants' invention.

For at least these reasons, Applicants are of the opinion that Nathanson is not relevant to the patentability of the subject invention.

Conclusion

Based on the foregoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at the number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Tanya M. Harding/
Tanya M. Harding, Ph.D.
Registration No. 42,630